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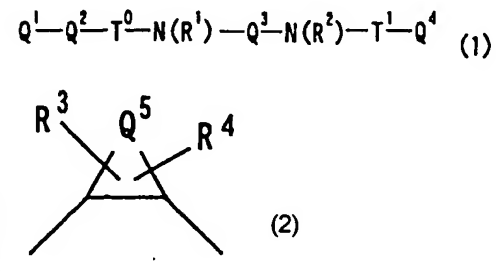
[続葉有]

(54) Title: DIAMINE DERIVATIVES

(54) 発明の名称: ジアミン誘導体



(1)

(2)

(57) Abstract: Compounds represented by the following general formula (1), salts thereof, solvates of the same or N-oxides of the same: Q^1-Q^2-T^0-N(R^1)-Q^3-N(R^2)-T^1-Q^4 (1) wherein R^1 and R^2 represent each hydrogen, etc.; Q^1 represents optionally substituted, saturated or unsaturated 5- or 6-membered hydrocarbyl, etc.; Q^2 represents a single bond, etc.; Q^3 represents the following group; (wherein Q^5 represents C_{1-8} alkylene, etc.); and T^0 and T^1 represent each carbonyl, etc. These compounds are useful as preventives and/or remedies for brain infarction, cerebral embolism, myocardial infarction, angina, pulmonary infarction, pulmonary embolism, Buerger's disease, bottom venous thrombosis, disseminated intravascular coagulation, thrombosis following artificial valve/joint replacement, thrombosis and reocclusion following circulation reconstruction, systemic inflammatory responsive syndrome (SIRS), multiple organ dysfunction (MODS), thrombosis in extracorporeal circulation or blood coagulation in collecting blood.

[続葉有]

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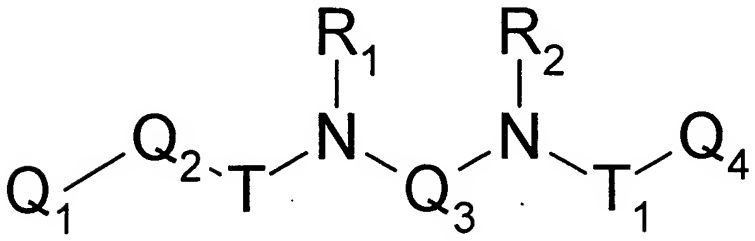
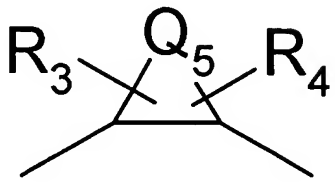
L7 ANSWER 2 OF 3 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-247888 [24] WPIX Full-text
CR 2003-247714 [24]; 2003-256264 [25]; 2003-312743 [30]
TI New diamine compounds are activated blood factor X inhibitors used for treating e.g. cerebral or myocardial infarction and angina.
PA (DAUC) DAIICHI PHARM CO LTD
PI WO 2003000680 A1 20030103 (200324)* JA 811 C07D401-12 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
EP 1405852 A1 20040407 (200425) EN C07D401-12
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
PRAI WO 2002-JP2683 20020320; JP 2001-187105 20010620;
JP 2001-243046 20010809; JP 2001-311808 20011009;
JP 2001-398708 20011228
TECH UPTX: 20030410



(I)



(i)

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I; T = C(O)) Are prepared e.g. by reacting an amine of formula (IV) with an acid of formula (V).

AB WO2003000680 A UPAB: 20040418
NOVELTY - Diamine compounds (I) are new.
DETAILED DESCRIPTION - Diamine compounds of formula (I) and their salts, solvates and N-oxides are new. R1, R2 = H, OH, alkyl or O-alkyl; Q1 = 5-6C carbocyclyl, 5-7 membered heterocyclyl or bi- or tri-cyclic carbocyclyl or heterocyclyl (all optionally unsaturated and optionally substituted);
Q2 = a bond, or divalent 5-6C carbocyclyl, 5-7 membered heterocyclyl or bi- or tri-cyclic carbocyclyl or heterocyclyl (all optionally unsaturated and optionally substituted); Q3 = a group of formula (i);
Q5 = 1-8C alkylene, 2-8C alkenylene or (CH2)mCH2ACH2(CH2)n; m, n = 0-3;
A = O, N, S, SO, SO2, NH, ONH, NHNH, SNH, SONH or SO2NH; R3, R4 = H, OH, alkyl (optionally substituted by CN, NH2, NHA, NAA, acyl, acylamino, O-alkyl, OH, COOH, COOAlk, NHCOOA, N-alkenylcarbamoyl, N-alkenyl-N-alkyl-carbamoyl, CONHO-alkyl, CON(A)OA, SO2A, CONH2, OCONH2, OCONHA, OCONAA, OCOHet, COHet, Ar1, NHSO2-alkyl, NHSO2Ar, CONHSO2-alkyl, CONHSO2Ar or optionally substituted CONHA or CONAA), alkenyl, alkynyl, halo, acyl, optionally substituted acylamino, O-alkyl, COOH, COO-alkyl, NHACOOA, NHACOOH, CONH2, CONHA, CONAA, N-alkenylcarbamoyl, N-alkenyl-N-alkyl-carbamoyl, CONHO-alkyl, CON(A)OA, CON(A)3, SO2A, COHet, Ar1, NHSO2-alkyl, NHSO2Ar, CONHSO2-alkyl, CONHSO2Ar, oxo, OCONH2, aralkoxy, O-alkyl-COOH, acyloxy, SO2Ar, SO2-alkyl-COO-alkyl, SO2-alkyl-COOH, acyl substituted by COO-alkyl, OH, O-alkyl, halo, COOH, NH2, acyloxy, NH-alkyl, N(alkyl)2, SO2-alkyl or optionally substituted CON(alkyl)2, COO-alkyl-O-alkyl or acyloxyalkylsulfonyl, SO2-alkyl-OH, SO2O-alkyl, SO2Het or optionally substituted SO2CON(alkyl)2, or R3 + R4 = 1-5C alkylene, 2-5C alkenylene, 1-5C alkylenoxy or carbonyldioxy;
Het = optionally substituted 3-6C heterocyclyl; Ar1 = aryl or heteroaryl;
Ar = aryl;

Q4 = Ar1, arylalkenyl, arylalkynyl, heteroarylalkenyl or optionally unsaturated bi- or tricyclic carbocyclyl or heterocyclyl (all optionally substituted);
T = CO or CS;
T1 = CO, SO2, COCONR11, CSCONR11, COCSNR11, CSCSNR11, COA1NR12, CONH, CSNH, CONHNH, COA2CO, COA3CONH, COC(=NORa)NRb, CS(=NORa)NRbCON=N, CSN=N, C(=NORc)CONRd, C(=NnReRf)CONRg or CS; R11, R12, Rb, Rd, Rg = H, OH, alkyl or O-alkyl; A1 = optionally substituted 1-5C alkylene; A2 = a bond or A1;
Ra = H, alkyl or alkanoyl;
Rc = H, alkyl, CO-alkyl, Ar or aralkyl, and Re, Rf = H, alkyl, CO-alkyl or CS-alkyl. ACTIVITY - Cerebroprotective; Anticoagulant; Cardiant; Antianginal; Respiratory; Anticoagulant; Thrombolytic; Vasotropic; Antiinflammatory.
MECHANISM OF ACTION - Factor X Inhibitor. In tests on rats, administration of N1-(4-chlorophenyl)-N2- ((1S,2R,4S)-4-((dimethylamino)carbonyl)-2-(((5-methyl-4,5,6,7-tetrahydrothiazolo(5,4-c)pyridin-2-yl)carbonyl)amino)cyclohexyl)ethanediam ide (Ia) (10 mg/kg orally) reduced blood FXa levels over 4 hours by 62-96 %.
USE - Used for treating and preventing e.g. cerebral infarction, cerebral embolism, myocardial infarction, angina, pulmonary, embolism, Buerger's disease, deep vein thrombosis, disseminated intravascular coagulation, thrombosis following artificial flap/hip replacement or during external circulation, reocclusion, systemic inflammatory reaction syndrome, multiple organ failure or blood coagulation during blood collection.

ABEX

UPTX: 20030410
ADMINISTRATION - Administration of (I) is 0.1-200 (preferably 0.5-100) mg/kg/day orally or by injection.

EXAMPLE - 1-Hydroxybenzotriazole monohydrate (71 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloric acid (100 mg) were added to N-((1Rasterisk,2Sasterisk)-2-aminocyclopropyl))-5- chloroindole-2-carboxamide (108 mg) and lithium 5-methyl-4,5,6,7- tetrahydrothiazolo(5,4-c)pyridine-2-carboxylate (124 mg) in dimethylformamide (3 ml) and the mixture was stirred at room temperature for 8 hours. Work-up including silica gel chromatography (methylene chloride:methanol = 10:1) gave 72 mg of N-(1Rasterisk,2Sasterisk)-2-(((5- chloroindol-2-yl)carbonyl)amino)cyclopropyl)-5-methyl-4,5,6,7- tetrahydrothiazolo(5,4-c)pyridine-2-carboxamide hydrochloride.